B5 22. (New) The method of claim 21, wherein said p63 gene product is ΔNp63 mRNA.

REMARKS

Claims 2-10, 13, and 14 are currently under examination. Claims 2, 4, 6 and 10 have been amended and claims 15-22 have been added. No new matter has been added by virtue of these amendments. The claim amendments are supported by the specification and claims as originally filed.

In particular, support for the amendments to claims 2, 6 and 10 can be found, for example, at page 8, line 35 to page 9, line 7, page 71, lines 10-14, page 71, line 36 to page 72, line 10, and page 72, lines 16-21, etc.

Support for the amendment to claim 4 can be found, for example, in claims 6-9 as originally filed, etc.

Support for new claims 15 and 17 can be found, for example, at page 19, etc.

Support for new claim 16 can be found for example, in claim 5 as originally filed, etc.

Support for new claims 18-22 can be found, for example, in Example XX at pages 129-134, etc.

Cancellation and/or amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of the present application. Applicant reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Rejection of Claims 2-10 under 35 U.S.C. § 112, Second Paragraph

Claims 2-10 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Specifically, claims 2, 6 and 10, and dependent claims thereof, are rejected as allegedly indefinite in the recitation of the phrase "a decrease in the level of said p63." The Action states

that this claim is indefinite because the amount of decrease needed to indicate malignant carcinoma is not known. Claims 2, 6 and 10 have been amended to specify that the decrease in the level of p63 gene product is compared to the level of p63 gene product in a control sample. In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 2-5 under 35 U.S.C. § 112, First Paragraph

Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, for reasons of enablement. In particular, the Office Action states that:

> [T]he specification, while being enabling for the detection of malignant carcinomas, does not reasonably provide enablement for the diagnosis of carcinomas, detection of the onset of cancer, and distinguishing cervical squamous versus cervical small cell undifferentiated carcinoma...There is a lack of enabling disclosure especially for how much of a decrease over normal tissue[] samples that would be an indication of a cancerous phenotype. (Office Action at 3).

The Action further cites the Wands Factors and states that the instant specification only provides initial experimentation to determine what levels of p63 protein are normal versus what levels are indicative of a cancerous phenotype (Wands Factors one and two). The Action also relies of Righi et al. (Diagn. Cytopathol. 17: 436-9 (1997)) for the teaching that there is a great deal of unpredictability and inaccuracy associated with the diagnosis of cancer using protein levels (Wands Factors four, five, and six). With respect to Wands Factor three, the Action states that the working examples are limited to the detection of p63 gene product by immunohistochemical methods and that such is not seen as sufficient to support the breadth of the claims wherein the scope of the claims encompasses diagnosis of cancer.

The rejection is respectfully traversed.

Applicants respectfully submit that the specification clearly provides sufficient enablement for detecting malignant carcinoma. The Examiner's attention is drawn, for example, to Examples XIX and XX starting at pages 117 and 129 of the specification, respectively. Example XIX shows that there is a strong association between strong p63 staining and malignant carcinoma, in particular having a squamous phenotype (see, e.g., page 120, line 26 to page 121, line 13, and Table I at page 124). In Example XX, the expression of p63 mRNA and p63 protein is assessed in normal and transformed prostate cell populations. The results demonstrate that the basal cell specific p63 is useful in the differential diagnosis of benign versus malignant lesions of

the prostate. In particular, Table 2 at page 132 shows that 48/48 samples of prostatic intraepithelial neoplasia were negative for p63 and that 126/130 invasive carcinoma samples were negative for p63 while in the 4 cases positive for p63 only about 2% of the cells were positive for p63. In addition, Table 3 at page 133 shows that p63 protein is expressed in nuclei of ~80% of normal basaloid prostate PrEC cells and that LNCaP, PC3, and DU145 cells do not express p63 protein by immunohistochemistry. Furthermore, Applicants respectfully submit that the specification clearly goes far beyond merely providing examples directed to detection of the p63 gene product by immunohistochemical methods. Indeed, the specification provides multiple working examples showing a strong correlation between a malignant phenotype and a decrease in the level of p63 as compared to a control sample. Accordingly, the specification provides much more than initial experimentation as alleged in the Action and therefore satisfies the requirements of the Wands Factors.

With respect to claim 10, the specification clearly provides sufficient enablement for distinguishing cervical squamous carcinoma from cervical small cell undifferentiated carcinoma. The Examiner's attention is drawn, for example, to Example XIX starting at page 117 of the specification. In Example XIX 236 cases of cervical carcinoma were examined including 181 squamous cell carcinomas and 14 small cell undifferentiated carcinomas. As shown in Table 1, 97% of the squamous cell carcinomas stained positive for p63 while p63 immonstaining was invariably absent in small cell undifferentiated carcinomas (see, e.g., page 120, line 26 to page 121, line 13, and Table I at page 124). Therefore, the specification clearly goes far beyond merely providing initial experimentation and thus satisfies the requirements of the Wands Factors.

Righi et al. is relied upon for the teaching that there is a great deal of unpredictability and inaccuracy associated with the diagnosis of cancer using protein levels. Applicants submit that, contrary to the teachings of Righi et al., it is common to look at the level of a gene product (e.g., mRNA or protein, etc.) in order to detect a cancer phenotype. Examples of cancer markers include prostate specific antigen (see e.g., Brawer, CA Cancer J. Clin. 49: 264-81 (1999)), prostate specific membrane antigen (see e.g., Holmes, Expert Opin Investig Drugs 10: 511-9 (2001)), cancer antigen-125 for the detection of ovarian cancer (see e.g., von Schlippe et al., Forum (Genova) 10: 383-92 (2000)), serum alpha-fetoprotein for the detection of hepatocellular carcinoma (see e.g., Ishii et al., Am. J. Gastroenterol 95: 1036-40 (2000) and Wong et al., Cancer

Lett. 156: 141-9 (2000)) or testicular cancer (see e.g., Yuasa et al., J. Androl. 20: 336-40 (1999)), and carcinoembryonic antigen for the detection of colorectal cancer (see e.g., Ito et al., Cancer Lett. 183: 195-203 (2002)).

The specification provides multiple working examples showing the strong correlation between the absence of p63 in cells and the presence of cancer phenotype in these cells. Thus, the specification is clearly enabling for the claimed invention. In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 6-9 and 13-14 under 35 U.S.C. § 102(a)

Claims 6-9 have been rejected under 35 U.S.C. §102(a) as being anticipated by Hall et al. (Carcinogenesis 21: 153-60 (2000)).

In particular the Office Action states that:

> Claims 6-9 are drawn to methods of detecting the onset of cancer in sub-columnar reserve cells (cervical, breast, prostate, kidney, testis, adrenal gland, brain, spleen, and thymus), by determining the level of p63 gene product (protein). Hall et al. disclose of the detection of p63 protein by immunohistochemical and immunoblot methods in breast, spleen, and kidney (pg 155 fig 3 and pag 156 fig 4). Furthermore, Hall et al. disclose that p63 (ΔNp63α) is also found in neoplastic tissues. Therefore, the invention as claimed in anticipated. (Office Action at 5)

The rejection is respectfully traversed.

Applicants submit that the claimed invention is entitled to a priority date that is earlier than the publication date of Hall et al., and thus, that this rejection is improper. The instant application is a continuation-in-part of U.S.S.N. 09/174,493 filed October 15, 1998 (hereinafter "the '493 application"). The '493 application discloses that p63 is detected in a wide range of tissues including breast, spleen and kidney (see e.g., page 19, lines 26-28 and Figure 24 and the accompanying description at page 18). The '493 application also discloses immunohistochemical analysis of p63 in a variety of tissues (see e.g., Example X at pages 109-110 and Figures 3-5). Furthermore, the '493 application discloses that p63 (ΔNp63α) is also found in neoplastic tissues (see e.g., page 11, lines 12-17). Therefore, the instant specification claims priority to an application which pre-dates the Hall et al. reference and contains teachings of the information for which the Hall reference is relied upon. Accordingly, the Hall et al.

reference does not anticipate the claimed invention because it is not a proper 35 U.S.C. §102(a) reference for the cited information. In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 13-14 have been rejected under 35 U.S.C. §102(a) as being anticipated by Hall et al. (Carcinogenesis 21: 153-60 (2000)).

In particular the Office Action states that:

> Claims 13 and 14 are drawn to a kit for diagnosing malignant carcinoma comprising p63 antibody. Hall et al. disclose of an antibody that is reactive to ΔNp63α. Therefore, the invention as claimed is anticipated. (Office Action at 5)

The rejection is respectfully traversed.

Applicants submit that the claimed invention is entitled to a priority date that is earlier than the publication date of Hall et al., and thus, that this rejection is improper. As stated above, the instant application claims priority as a continuation-in-part to the '493 application. The '493 application discloses an antibody reactive to ΔNp63α (see e.g., Example X, page 109, first paragraph). Therefore, the instant specification claims priority to an application which pre-dates the Hall et al. reference and contains teachings of the information for which the Hall reference is relied upon. Accordingly, the Hall et al. reference does not anticipate the claimed invention because it is not a proper 35 U.S.C. §102(a) reference for the cited information. In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 2-6 and 10 under 35 U.S.C. § 103(a)

Claims 2-6 and 10 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hall et al. (Carcinogenesis 21: 153-60 (2000)) in view of Parsa et al. (J. Invest. Dermatol. 113: 1099-1105 (1999)).

The Action states that:

> Hall et al. disclose of detecting p63 protein by using immunohistochemical and immunoblot techniques. In addition, Hall et al. also disclose that the tissue types that are involved are breast, kidney, and spleen (see fig 3 pg 155). Hall et al. do not disclose of detection of p63 in squamous cell carcinomas. Parsa et al., however, do disclose of detection of p63 in squamous cell carcinomas (see abstract). Both references disclose of p63's homology to p53, a known cancer marker. (Office Action at 7)

The rejection is respectfully traversed.

As discussed above, Applicants submit that the claimed invention is entitled to a priority date that is earlier than the publication date of Hall et al. In addition, the claimed invention is also entitled to an earlier priority date than the publication date of Parsa et al. In view thereof, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 832-1000.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our **Deposit Account No. 06-1448**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

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Marked-up version of claims showing changes made:

Please amend claims 2, 4, 6 and 10 as set forth below and add new claims 15-22 as follows:

2. (Amended) A method for [diagnosing] detecting malignant carcinoma[s], comprising:

(a) obtaining a [biopsy sample of] tissue sample from a patient;

(b) determining the level of a p63 gene product in said patient sample;

(c) comparing the level of said p63 gene product in said [biopsy] patient sample with the level of said p63 gene product in a control sample of cells;

wherein a [decrease in the] lower level of said p63 gene product in said patient sample as compared to the control sample is indicative of the presence of malignant carcinoma[s in said biopsy sample].

4. (Amended) A method of claim 2, wherein said control sample is selected from the group comprising basal epithelial cells, immature squamous cells, ME 180, sub-columnar reserve cells and human foreskin keratinocytes.

6. (Amended) A method for detecting [the onset of] cancer in tissues containing sub-columnar reserve cells, comprising:

(a) obtaining a [biopsy sample of] tissue sample from a patient;

(b) determining the level of a p63 gene product in said patient sample;

(c) comparing the level of said p63 gene product in said [biopsy] patient sample with the level of said p63 gene product in a control sample of cells;

wherein a [decrease in the] lower level of said p63 gene product in said patient sample as compared to the control sample is indicative of the [onset] presence of cancer in said tissues.

10. (Amended) A method for distinguishing cervical squamous carcinoma from cervical small cell undifferentiated carcinoma, comprising:

(a) obtaining a [biopsy sample of] cervical tissue sample from a patient;

(b) determining the level of a p63 gene product in said patient sample;

(c) comparing the level of said p63 gene product in said [biopsy] patient sample with the level of said p63 gene product in a control sample of cervical squamous carcinoma cells;

wherein a decrease in the level of said p63 gene product in said patient sample as compared to the control sample is indicative of small cell undifferentiated carcinoma.

15. (New) The method of claim 2, wherein said p63 gene product is selected from the group consisting of TAp63α, TAp63β, TAp63γ, ΔNp63α, ΔNp63β and ΔNp63γ.

16. (New) The method of claim 10, wherein the level of said p63 gene product is determined by a method selected from the group comprising RT-PCR, immunoblotting, immunoprecipitation, and sandwich immunoassay.

17. (New) The method of claim 10, wherein said p63 gene product is selected from the group consisting of TAp63α, TAp63β, TAp63γ, ΔNp63α, ΔNp63β and ΔNp63γ.

18. (New) A method for distinguishing benign prostate lesions from malignant prostate lesions, comprising:

(a) obtaining a prostate tissue sample from a patient;

(b) determining the level of a p63 gene product in said patient sample;

(c) comparing the level of said p63 gene product in said patient sample with the level of said p63 gene product in a control sample of basaloid prostate cells;

wherein a decrease in the level of said p63 gene product in said patient sample as compared to the control sample is indicative of small cell undifferentiated carcinoma.

19. (New) The method of claim 18, wherein the level of said p63 gene product is determined by a method selected from the group comprising RT-PCR, immunoblotting, immunoprecipitation, and sandwich immunoassay.

20. (New) The method of claim 19, wherein said p63 gene product is selected from the group consisting of TAp63α, TAp63β, TAp63γ, ΔNp63α, ΔNp63β and ΔNp63γ.

21. (New) The method of claim 19, wherein the level of said p63 gene product in said patient sample is at least 2000-fold lower than the level of p63 gene product in said control sample.

22. (New) The method of claim 21, wherein said p63 gene product is ΔNp63 mRNA.